REMARKS

In accordance with the present invention, there is provided three-dimensional structural information related to farnesoid X receptors (FXR). In a particular aspect, there are provided compositions comprising an exemplary ligand binding domain of FXR in crystalline form (as described, for example, by structure coordinates obtained by X-ray crystallography), and computers utilizing such structure coordinates to provide information regarding the ligand binding domain of FXRs and ligands therefor. In another aspect, the invention provides methods of utilizing such structure coordinates for screening compounds to identify those which are capable of binding FXR, and those which are FXR agonists, partial agonists and antagonists.

By the present communication, claims 14, 19 and 31 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. For example, support for amended claim 14 can be found at paragraph [0153].

Upon entry of the amendments submitted herewith, claims 1-3, 6-8, 10-15, 18-22 and 31-33 will remain pending in the application, with claims 14-15 and 18-20 under active prosecution, and claims 1-3, 6-8, 10-13, 21-22 and 31-33 withdrawn from consideration, subject to a request for rejoinder thereof. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination, is presented in the Listing of Claims, beginning on page 2 of this communication, with an appropriate status identifier for each claim.

Claim Objections

The objections to claims 14, 15 and 18-20 for alleged informalities therein are respectfully traversed. Applicants respectfully submit that the objections do not apply to the instant claims.

Rejections under 35 U.S.C. § 112

Written description

The rejection of claims 14, 15 and 18-20 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the disclosed invention allegedly contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Office Action, p. 4, ll. 10-11).

Contrary to the Examiner's assertion, it is respectfully submitted that the specification provides substantial information to convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14, as amended herein, and claims 15 and 18 dependent therefrom, are directed to methods of screening molecules to determine those which are capable of binding to a farnesoid X receptor (FXR) molecule. The claimed methods require:

> modeling a test molecule that potentially interacts with a ligand binding domain of a farnesoid X receptor (FXR) comprising amino acid residues 248 – 476 of SEQ ID NO:1,
>
> wherein said ligand binding domain is defined by a plurality of structure coordinates of the ligand binding domain of a FXR molecule or a fragment thereof, and
>
> wherein said structure coordinates are based on X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex, or a homologue of said FXR molecule or molecular complex,
>
> whereby those molecules which lack repulsive electrostatic interaction with FXR molecule in their bound state are capable of binding to a farnesoid X receptor (FXR) molecule therefor.

Thus, the invention methods require modeling a test molecule with a defined ligand binding domain of a farnesoid X receptor, then determining if the test compound is capable of binding to

a farnesoid X receptor based on the lack of repulsive electrostatic interaction with FXR molecule in their bound state.

Contrary to the Examiner's assertion that "[t]he specification discloses only a single species of claimed genus method" (Office Action, p. 6, l. 9), the present invention discloses substantial information for screening compounds capable of binding to any FXR. As described at paragraph [0005], "[t]he FXR members share two structurally conserved domains; [one of them] is a ligand binding domain (LBD) that binds small lipophilic hormones (Evans R M. Science. 240(4854), 889-95)." The present invention provides that "[t]he LBD of SEQ ID NO:1 corresponds to approximately C-terminal amino acid residues 248-476" (paragraph [0046]). Thus the present invention provides an exemplary ligand binding domain. Utilizing the exemplary LBD, one skilled in the art can model any compound against the exemplary LBD for determination of the ability thereof to bind a FXR molecule (whereby those compounds which lack repulsive electrostatic interaction with FXR molecule in their bound state are capable of binding to a farnesoid X receptor (FXR) molecule).

Claim 15 further defines Applicants invention by requiring certain structure coordinates (as set forth in Appendix 1 or a portion thereof). Claim 18 further defines Applicants invention by requiring a method to develop a test molecule using a computer algorithm to predict a three-dimensional representation of said test molecule interacting with a FXR.

Similarly, claim 19, as amended herein (and claim 20 dependent therefrom), further define Applicants' invention by requiring a method of screening compounds to determine those with agonist, partial agonist or antagonist activity with respect to a farnesoid X receptor (FXR) molecule. The claimed method comprises:

> (a) modeling a test compound that potentially interacts with the ligand binding domain of said FXR molecule comprising amino acid residues 248 – 476 of SEQ ID NO:1,

wherein said ligand binding domain is defined by a plurality of structure coordinates of a crystalline form of the ligand binding domain of a FXR molecule or a fragment thereof, and

wherein said plurality of structure coordinates are based on X-ray diffraction data obtained from crystals of said FXR molecule or molecular complex, or a homologue of said FXR molecule or molecular complex; and

(b) determining the ability of said test compound to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist,

whereby those compounds which bind and alter the activity of farnesoid X receptor (FXR) molecule are identified as agonists or partial agonists, and those compounds which bind but do not alter the activity of farnesoid X receptor (FXR) molecule are identified as antagonists therefor.

Thus, all that is required for any person skilled in the art to carry out the claimed method (as fully described in the specification) is to model a test compound with the exemplary ligand binding domain (i.e., a molecule comprising amino acid residues 248 – 476 of SEQ ID NO:1), then determine the ability of the test compound to modulate the activity of FXR (i.e., as an agonist, partial agonist or antagonist).

Based on the modeling described in Applicants' specification utilizing an exemplary ligand binding domain and the description of various uses thereof in the application as filed, one skilled in the art would readily recognize that Applicants were in possession of the invention, as claimed, at the time the present application was filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Enablement

The rejection of claims 14, 15 and 18-20 under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the specification does not enable any person skilled in the art to which it pertains to make and/or use the invention commensurate in scope with these claims (Office Action, p. 9, ll. 5-6).

It is respectfully submitted that the specification enables any person skilled in the art to make and/or use the invention commensurate in scope with the claims. Indeed, as acknowledged by the Examiner (see Office Action, p. 8, item 7) the specification is enabling for "a method of predicting a molecule capable of binding to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO:1); or identifying a compound with agonist, partial agonist, or antagonist activity to a human FXR ligand binding domain...."

In addition, the present claims are supported by a disclosure which provides substantial information for screening compounds capable of binding to any FXR because "[t]he FXR members share two structurally conserved domains; [one of them] is a ligand binding domain (LBD) that binds small lipophilic hormones (Evans R M. Science. 240(4854), 889-95)." Thus utilizing the exemplary LBD in the claimed method, one skilled in the art can model any molecules or compounds against the exemplary LBD for determination of:

- the ability of the test compound to bind to a FXR molecule, or
- the agonist, partial agonist, or antagonist activity of the test compound with respect to a FXR molecule or fragment thereof.

Applicants respectfully submit that all claims are fully supported by the specification. Moreover, undue experimentation is not required to make and/or use the claimed invention, especially in light of the description of relevant structure coordinates, the identification of an

exemplary ligand binding domain of farnesoid X receptor and the description of various uses thereof in the application as filed.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejection under 35 U.S.C. § 101

The rejection of claims 14, 15 and 18-20 under 35 U.S.C. § 101, as allegedly being directed to non-statutory subject matter is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the method of claims 14, 15 and 18-20 does not produce a "useful, concrete and tangible result," (Office Action, p. 15, l. 7) that there is "no active method step that selects for compounds that bind and/or modulate the protein" (Office Action, p. 15, ll. 11-12).

Consistent with the preceding discussion, claim 14, as amended herein, is directed to a method of screening molecules to determine those which are capable of binding to a farnesoid X receptor (FXR) molecule. A test molecule is first modeled against a defined ligand binding domain and then determined ("selected") to be capable of binding to a farnesoid X receptor based on defined criteria, i.e., the lack of repulsive electrostatic interaction with FXR molecule in their bound state.

Similarly, claim 19, as amended herein, is directed to a method of screening compounds to determine those with agonist, partial agonist, or antagonist activity with respect to a farnesoid X receptor (FXR) molecule. The test compounds, after modeling, are then evaluated by determining their ability to modulate the activity of said FXR molecule in the optional presence of a known FXR agonist; the compounds that bind and alter the activity of farnesoid X receptor (FXR) molecule are identified as agonists or partial agonists, and the compounds that bind but do not alter the activity of farnesoid X receptor (FXR) molecule are identified as antagonists.

Any potential molecules can be so modeled and identified as either meeting the desired criteria as in claim 14 or 19, or not. Either way, the claimed method produces a useful, concrete and tangible result.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Rejection under 35 U.S.C. § 102

The rejection of claims 14, 15 and 18-20 under 35 U.S.C. § 102(b), as allegedly being anticipated by McKinney (Environmental Health Perspectives, 1989, volume 82, page 323-336) is respectfully traversed. Applicant respectfully submits that the rejection does not apply to the instant claims.

CONCLUSION

In view of the above amendments and remarks, applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: November 21, 2008

By _____

FOLEY & LARDNER LLP
Customer Number: 30542
Telephone: 858-847-6711
Facsimile: 858-792-6773

Stephen E. Reiter
Attorney for Applicant
Registration No. 31,192